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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,861	04/25/2001	Daniel Dupret	58763.000013	4902

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	18

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,861	DUPRET ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *37-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36 and 42-49* is/are rejected.

7)☒ Claim(s) *10-13,22-24,27-29,31,33-35 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Examiner of record has been changed. All further correspondence regarding this application should be directed to Examiner Young J. Kim whose Group Art Unit is 1637.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on August 12, 1998. It is noted, however, that applicant has not filed a certified copy of the FR 98/10338 application as required by 35 U.S.C. 119(b).

Additionally, Applicants have not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of any foreign application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date.

Information Disclosure Statement

The references cited in the IDS received on July 30, 2002 (Paper No. 7) have been received and the references listed therein have been considered and the signed copy of the PTO-1449 provided herein.

As to Applicants' request for clarification in the statement in the previous Office Action regarding the IDS, the statement communicated the fact that the IDS statement and the PTO-1449 have been placed in the file, but the references listed therein (PTO-1449) have not been considered because the references were missing. The present Examiner is not aware of the actions committed by the previous Examiner. However, the Office acknowledges the receipt of the references in the IDS.

The citation of reference number 62 is erroneous. The authors of the reference has been corrected to Rouwendal et al.

Drawings

The objection to the specification for lacking Brief Description of the Figures, made in the Office Action mailed on September 26, 2002 is withdrawn in view of the Amendment received on December 30, 2002, amending the specification to include the description.

The objection to the specification for failing to contain a proper Abstract, made in the Office Action mailed on September 26, 2002 is withdrawn in view of the Amendment received on December 30, 2002.

Claim Objections

The objection of claims 4-10, 22, 29, and 30 under 37 CFR 1.75(c) as being improper form for containing improper multiple dependent claims, made in the Office Action mailed on September 26, 2002 is withdrawn in view of the Amendment received on December 30, 2002, amending the claims to a proper form.

The objection of claims 1 and 11 for minor informality in their claim language, made in the Office Action mailed on September 26, 2002 is withdrawn in view of the Amendment received on December 30, 2002, amending the claims to a proper form.

The objection of claims 1-3, 11-21, 23-28, and 31-36 for minor informality in their claim language, made in the Office Action mailed on September 26, 2002 is withdrawn in view of the Amendment received on December 30, 2002, amending the claims to a proper form.

Claim Objections – New Grounds

Claims 10-13, 22, 23, 27, 28, 29, 31, 33-35, and 43 are objected to because of the following informalities: a claim which depends from a dependent claim should not be separated from that dependent claim by any claim which does not also depend from the dependent claim (see MPEP 608.01(n), at 600-63; *Claim Form and Arrangement*). Appropriate correction is required.

Claim 24 recites the term, "wild gene." It is believed that the correct terminology for the term is "wild-type gene." Appropriate correction is required.

Claim 33 is objected to for the recitation of the phrase, "at step (c) are separated from the assembly matrix *thanks to* a marker present." Rephrasing is required.

Claim Rejections - 35 USC § 112

The rejection of claims 1-36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on September 26, 2002 is withdrawn in view of the Amendment received on December 30, 2002.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 23, 25, 30, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 23 are indefinite because it is unclear to which enzyme the term, "enzyme" is referring to. The method further comprises an enzyme (claim 18) as well as having a thermostable ligase, rendering the claims confusing in to which enzyme the term is referring.

Claim 25 is indefinite for the use of the term, "synthetic," because it is unclear what polynucleotide sequences are determined to be synthetic since all polynucleotides are "synthesized."

Claim 30 is indefinite for the recitation of the term, "initiated oligonucleotides," because it is unclear what parameters must be met for an oligonucleotide to be considered initiated and the specification does not clearly define the term.

Claim 36 is improperly multiple dependent because it depends on claim 1 twice. Claim 36 also recites the term, "one or several restricted banks." It is unclear what this term means. For the purpose of prosecution, the term is assumed to mean "one or several banks of polynucleotide sequences prepared from prior fragmentation reaction."

Claim Rejections - 35 USC § 102

The rejection of claims 1-3, 11-18, 20, 24-28, and 31-36 under 35 U.S.C. 102(e) as being anticipated by Stemmer et al. (US 2001/0049104 A1, December 6, 2001), made in the Office Action mailed on September 26, 2002 is withdrawn in view of careful reconsideration of the application and the arguments made in the Amendment received on December 30, 2002.

Rejections – New Grounds

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-18, 20-36, 42-44, and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer et al. (Proc. Natl. Acad. Sci., USA 1994, vol. 91, pages 10747-10751; IDS ref# 63).

Stemmer et al., herein referred to as Stemmer reference, disclose an *In vitro* (claim limitation 34, 35, and 44) DNA shuffling method by random fragmentation and reassembly *In vitro* recombination for molecular evolution (Abstract). The method disclosed by Stemmer reference comprises as follows:

a) providing fragments of nucleic acids (or oligononucleotides) derived from a bank of at least two polynucleotide sequences (page 10747, "Materials and Methods", page 10748 1st column; claim limitation 1-a and 25);

b) hybridizing the fragments to an assembly matrix so that fragments are oriented for ligation with each other (figure 1-B; claim limitation 1-b and 14); and

c) ligating the oriented fragments to form a recombinant polynucleotide sequence (figure 1-C and 1-D; page 10747 "Materials and Methods- *PCR without primers*"; claim limitation 1-c and 15).

The instant specification defines the term, "assembly matrix" as single- or double-stranded nucleic acids which could serves as a template for two oligonucleotides to hybridize

adjacently (page 4, claim 1-c, claim 28, and 29). Figure 1-B of the Stemmer reference disclose at least one nucleic acid sequence which would serve as a template which allow the hybridization of two adjacent nucleic acid fragments, therefore, considered as an assembly matrix.

The method of Stemmer reference comprises fragmenting the polynucleotide sequences via random DNase I digestion (page 10747, "Materials and Methods *–DNase I Digestion*", Abstract-line 7, figures 1-A through D; claim limitation 2, 16, 17, 26, 27, 31, 42, and 43), as well as selecting the resulting recombinant polynucleotide sequences (page 10747 "Materials and Methods- *PCR without primers*"; claim limitation 3). The starting library of the double stranded nucleic acid is denatured prior to reassembly reaction with the assembly matrix at 94°C for 60 seconds, producing single stranded nucleic acid, some of which would be assembly matrices (page 10747 "Materials and Methods- *PCR without primers*"; claim limitation 4-7, 28, and 29). Figures 1-B & 1-C evidence the repeat of the hybridization of adjacent fragments to the assembly matrix (claim limitation 8 and 9). Figure 1-D and page 10750, 2nd column, 2nd paragraph evidence the subjecting of resulting recombinant polynucleotide to another cycle of fragmentation (claim limitation 10, 24, 32, and 36). The resulting recombinant polynucleotide sequences are amplified separated and cloned for selection (page 10747, "Materials and Methods *– PCR with Primers & Cloning and Analysis*, Figure 2, page 10750 *Technical Issues*; claim limitation 11-13 and 49). Addition of restriction enzyme is added in order to cleave the single stranded sequences at the ends of the recombinant polynucleotides (page 10747, "Materials and Methods – *PCR with Primers & Cloning and Analysis*, bottom; claim limitation 18, 20, 22, and 23). The amplified recombinant product is disclosed as containing a restriction site (or marker assisted) allowing the isolation of the product (via gel purification) from the non-recombinant

templates (page 10747, *Materials and Methods – Cloning and Analysis*; claim limitation 33). The method employs a *Taq* DNA polymerase which is also considered as a ligase (since it has a ligase function), active at high temperature (claim limitation 21). The starting initial bank of polynucleotides are amplified with primers (or initiated oligonucleotides; page 10747 "*Materials and Methods – Substrate Preparation*; claim limitation 30).

Therefore, Stemmer reference anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

The rejection of claim 19 under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (US 2001/0049104 A1 December 6, 2001) in view of Prudent et al. (US 6,348,314, February 19, 2002), made in the Office Action mailed on September 26, 2002 is withdrawn in view of careful reconsideration of the application and the arguments made in the Amendment received on December 30, 2002.

The rejection of claims 21 and 23 under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (US 2001/0049104 A1 December 6, 2001) in view of Auerbach (US 5,614,389 A, March 25, 1997), made in the Office Action mailed on September 26, 2002 is withdrawn in view of careful reconsideration of the application and the arguments made in the Amendment received on December 30, 2002.

Rejection – New Grounds

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (Proc. Natl. Acad. Sci., USA 1994, vol. 91, pages 10747-10751) in view of Rouwendal et al. (Biotechniques, 1993, vol. 15, no. 1, pages 68-70 and 72-75).

Claims 45-48 are drawn to an embodiment of claim 1 wherein, the adjacent nucleic acid fragments are ligated without a polymerase.

Stemmer et al., herein referred to as Stemmer reference, disclose an *In vitro* DNA shuffling method by random fragmentation and reassembly *In vitro* recombination for molecular evolution (Abstract). The method disclosed by Stemmer reference comprises as follows:

a) providing fragments of nucleic acids (or oligononucleotides) derived from a bank of at least two polynucleotide sequences (page 10747, "Materials and Methods", page 10748 1st column; claim limitation 1-a);

b) hybridizing the fragments to an assembly matrix so that fragments are oriented for ligation with each other (figure 1-B; claim limitation 1-b); and

c) ligating the oriented fragments to form a recombinant polynucleotide sequence (figure 1-C and 1-D; page 10747 "Materials and Methods- *PCR without primers*"; claim limitation 1-c).

Stemmer et al. do not employ polymerase in the ligation of the two adjacent nucleic acid sequences.

Rouwendal et al. disclose a well known technique of LCR (ligation chain reaction) and its application in ligating adjacent nucleic acids annealed to a single stranded nucleic acid template via use of a thermostable DNA ligase (limitation claims 45, 46, and 48). Rouwendal et

al also suggest that such ligation method would be useful in producing mutagenic (or recombinant) products (page 70, 3rd column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the suggestion of Rouwendal et al. into the teachings of Stemmer et al. to arrive at the claimed invention for the following reasons.

Initially, it is a well-known fact that a DNA polymerase comprises a ligase function. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the use of a polymerase for the use of a ligase under substitution of equivalence. The result sought by the Applicants is clearly the same as that of Stemmer et al. since claim 47 of the instant application require that after the ligation of the adjacent nucleic acids, amplification (via use of a polymerase) be conducted, the teaching of which is also taught by Rouwendal et al. (page 70, 3rd column, 3rd paragraph; claim limitation 47). Additionally, Rouwendal et al. would have reasonably motivated an ordinarily skilled artisan, at the time the invention was made, to substitute their teaching because the artisans, like Stemmer et al., also endeavored in molecular evolution for generating proteins of advantageous traits.

Therefore, the invention as claimed is obvious over the cited references.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (Proc. Natl. Acad. Sci., USA 1994, vol. 91, pages 10747-10751) in view of Gary et al. (The Journal of Biological Chemistry, 1997, vol. 272, no. 39, pages 24522-24529).

Stemmer et al., herein referred to as Stemmer reference, disclose an *In vitro* DNA shuffling method by random fragmentation and reassembly *In vitro* recombination for molecular evolution (Abstract). The method disclosed by Stemmer reference comprises as follows:

a) providing fragments of nucleic acids (or oligononucleotides) derived from a bank of at least two polynucleotide sequences (page 10747, "Materials and Methods", page 10748 1st column; claim limitation 1-a);

b) hybridizing the fragments to an assembly matrix so that fragments are oriented for ligation with each other (figure 1-B; claim limitation 1-b); and

c) ligating the oriented fragments to form a recombinant polynucleotide sequence (figure 1-C and 1-D; page 10747 "Materials and Methods- *PCR without primers*"; claim limitation 1-c).

The instant specification defines the term, "assembly matrix" as single- or double-stranded nucleic acids which could serves as a template for two oligonucleotides to hybridize adjacently (page 4, claim 1-c, claim 28, and 29). Figure 1-B of the Stemmer reference disclose at least one nucleic acid sequence which would serve as a template which allow the hybridization of two adjacent nucleic acid fragments, therefore, considered as an assembly matrix.

The method of Stemmer reference comprises fragmenting the polynucleotide sequences via random DNase I digestion (page 10747, "Materials and Methods –*DNase I Digestion*", Abstract-line 7, figures 1-A through D), as well as selecting the resulting recombinant polynucleotide sequences (page 10747 "Materials and Methods- *PCR without primers*"). Addition of restriction enzyme is added in order to cleave the single stranded sequences at the ends of the recombinant polynucleotides (page 10747, "Materials and Methods – *PCR with Primers & Cloning and Analysis*, bottom; claim limitation 18, 20, 22, and 23).

Stemmer reference do not teach the use of Flap endonuclease for cleaving single stranded sequences at the ends of the recombinant polynucleotides.

Gary et al. disclose the function of FEN-1 as being Flap endonuclease which cleaves single stranded sequences.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the use of restriction enzyme of Stemmer et al. with that of Flap endonuclease to cleave the single stranded sequences at the ends of the recombinant polynucleotides for the substitution of equivalent. The motivation to use an enzyme to cleave the single stranded sequences at the ends of the recombinant polynucleotides is disclosed as being desired to produce non-heterogeneous recombinant products (i.e., containing non-recombinant single stranded regions; page 10747 *Materials and Methods – PCR without Primers*).

Therefore, the invention as claimed is obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (703) 308-9348. The Examiner can normally be reached from 8:30 a.m. to 7:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (703)-308-3905. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (703) 308-1119. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. The Fax number is (703) 746-

3172. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Young J. Kim

7/23/03

JEFFREY SIEW
PRIMARY EXAMINER
7/24/03